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(54) 4a-Substituted avermectin derivatives

4-a-Substutierte Avermectinderivate

4-a-Substitué dérivés d'avermectine

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EP-A- 0 074 758 **EP-A- 0 303 933**

- **J. Agric. Food Chem., Vol. 42, No.8,1994, 1786-1790**

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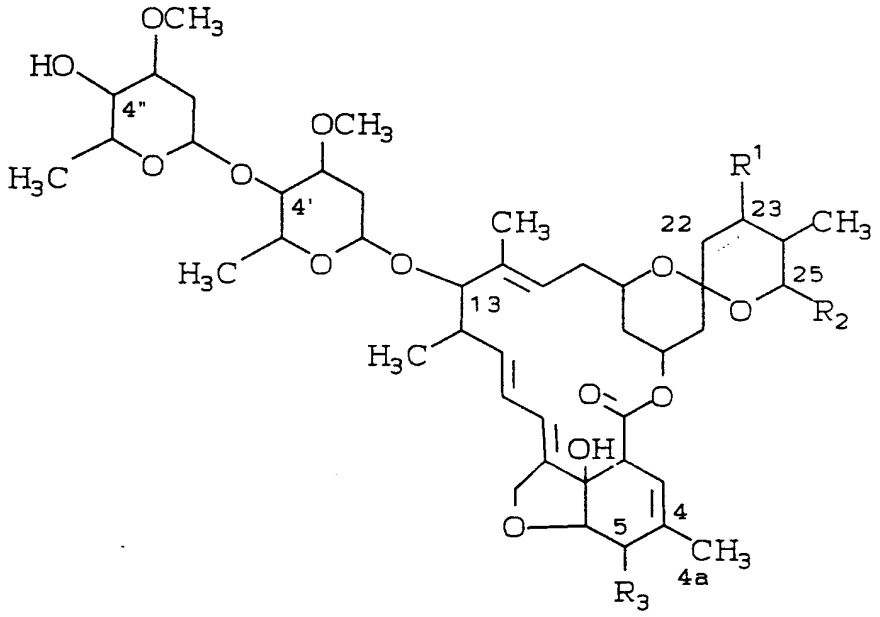
Description

BACKGROUND OF THE INVENTION

The avermectins (previously referred to as C-076 compounds) are a series of compounds produced by fermentation of avermectin producing-strains of Streptomyces avermitilis and derivatives thereof. The morphological characteristics of the culture are completely described in U.S. Pat. No. 4,310,519. The production, isolation, and structure determination of the avermectins are fully described in Albers-Schonberg et al J. Am. Chem. Soc. 1981, 103, 4216-4221 and references cited therein. The conversion of natural avermectin B_1 to 22,23-dihydro-avermectin B_1, the potent broad spectrum anthelmintic agent known as ivermectin, has also been described in the literature (Chabala et al J. Med. Chem. 1980, 23, 1134-1136). The naturally occurring avermectins and the instant derivatives thereof have a very high degree of anthelmintic and anti-parasitic activity.

The naturally occurring avermectins are a series of macrocyclic lactones which are substituted at position 13 with a disaccharide consisting of two oleandrose residues. The natural compounds have the following general structure:



wherein the broken line indicates a single or double bond at the 22,23-position and;

R_1 is hydroxy and is present only when said broken line indicates a single bond;
R_2 is iso-propyl or sec-butyl; and
R_3 is methoxy or hydroxy.

There are eight major natural avermectin compounds, designated A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. These designations are based on the structure of the individual compounds as shown in the following table (referring to the foregoing structural formula).

Compound	broken line	R_1	R_2	R_3
A1a	22,23-double bond	----	sec-butyl	--OCH_3
A1b	22,23-double bond	----	iso-propyl	--OCH_3
A2a	22,23-single bond	--OH	sec-butyl	--OCH_3
A2b	22,23-single bond	--OH	iso-propyl	--OCH_3
B1a	22,23-double bond	----	sec-butyl	--OH
B1b	22,23-double bond	----	iso-propyl	--OH
B2a	22,23-single bond	--OH	sec-butyl	--OH
B2b	22,23-single bond	--OH	iso-propyl	--OH

The avermectins are generally isolated as mixtures of the a and b components (typically ≥80% a and ≤20% b). Such compounds differ only in the nature of the R_2 substituent and this minor structural difference has been found to have very little effect on the chemical reactivity or biological activity of the compounds. Thus although the a and b components can be separated from each other by chromatography this is not necessary and hence is not normally done. The presence of a mixture of a and b components is indicated by dropping the a or b from the designation of the compound. A mixture of avermectin B1a and avermectin B1b is thus referred to as avermectin B1.

A related family of natural products is known as the milbemycins. The milbemycins have the same basic structure as the avermectins but have no substitution at position 13 and have a methyl or ethyl group at position 25 (R_2 = methyl or ethyl rather than isopropyl or sec-butyl as in the avermectins). The milbemycins and the fermentation conditions used to prepare them are described in U.S. Pat. No. 3,950,360. Closely related 13-deoxy-avermectin aglycones are prepared by chemical modification of the natural avermectins and have been described in U.S. Pat. Nos. 4,171,134 and 4,173,571. Avermectin aglycones, which may also be used as starting material for the instant compounds are disclosed in U.S. 4,206,205. U.S. Patent 4,457,920 described 4a-derivatives of avermectin compounds in which the 4a-substitutents are hydroxy, acetyloxy, benzoyloxy, pyridinyl carbonyloxy, pyrrolyl carbonyloxy or carboxyethanoyloxy. This reference also discloses the preparation of the 4a-hydroxy compounds which are the starting materials for the instant compounds.

Japanese patent publication 02,017,191 also describes compounds with 4a-substituents. The 4a-substitutents disclosed include azido, halo, cyano, alkanoyloxy, alkoxy, and nitrogen and sulfur substituted derivatives.

Recently a number of related compounds have been described in European Patent Application EPO 170,006 and U.K. aplication 2,166,436 (see also Carter et al, J. Antibiotics 1988, 41, 519-529). These compounds are essentially 13-deoxy-avermectin aglycones in which the R_2 side chain contains a double bond and, in some cases, includes additional carbon atoms.

Chemically modified derivatives of this group of compounds have recently become known. In particular compounds containing a N-methoxyimino substituent attached to the C-23 position are described in UK Patent Application GB 2 192 630 A and European Patent Application 0 237 341 A1. Moxidectin is the generic name for a compound of this group with the chemical name [6R,25S(E)]-5-0-demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoximino) Milbemycin B.

Recent publications have described the synthesis of avermectin A1a (Danishefsky et al, J. Am. Chem. Soc. 1989, 111, 2967) and avermectin B1a (Hanessian et al, J. Am. Chem. Soc. 1986, 108, 2776). Research on deconjugation and epimerization of avermectin C-2 stereoisomers is described in the two synthetic publications cited above as well as in Hanessian et al (J. Am. Chem. Soc. 1987, 109, 7063) and Fraser-Reid et al (J. Am. Chem. Soc. 1987, 109, 933).

The avermectins are highly potent anthelminthic and antiparasitic agents and are relatively non-toxic to most mammalian species. However, the avermectins are highly toxic to certain mammalian species and this fact precludes the use of avermectins for some applications. In addition, the avermectins are ineffective against some parasites and resistant strains of previously susceptible parasites may evolve. Thus it is desirable to discover novel avermectin analogs with improved activity and/or lower mammalian toxicity.

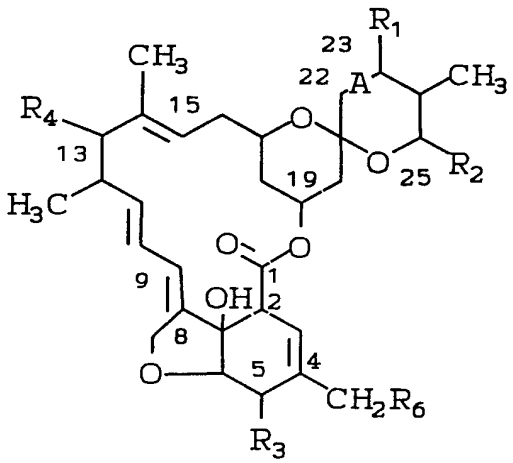
SUMMARY OF THE INVENTION

The instant invention is concerned with avermectin compounds which are substituted at the 4a-position by a variety of oxygen containing substituents in which the substituent is connected to the 4a-methyl group through the oxygen atom. Thus, it is an object of this invention to describe such 4a-substituted compounds. It is a further object to describe

the procedures for the preparation of such compounds. A still further object is to describe the use of such compounds as antiparasitic and anthelmintic agents. A still further objective is to describe compositions containing such compounds for use as antiparasitic and anthelmintic agents. Still further objects will become apparent from a reading of the following description.

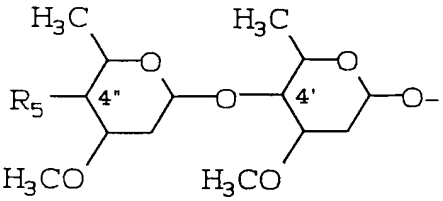
DESCRIPTION OF THE INVENTION

The compounds of the instant invention are best realized in the following structural formula.



where

A is a 22,23 single bond or a double bond;
R_1 is hydrogen provided that R_1 is present only when A is a single bond;
R_2 is isopropyl or sec-butyl;
R_3 is hydroxy;
R_4 is



where
R_5 is N-acetylamino or N-methyl-N-acetylamino; and
R_6 is hydroxy, acetoxy, benzoyloxy, nicotinoyloxy, or methoxyethoxymethoxy.

Above structural formula is shown without a definitive sterochemistry. However, during the course of the synthetic procedures used to prepare such compounds, the products of such procedures can be a mixture of stereoisomers. In particular, the substituents of the stereoisomers at the 4"-,4'-,13-,23-,24-, and 25-positions may be oriented either α or β- representing such groups being below or above the general plane of the molecule, respectively. In each such case both the α- and β-configurations are intended to be included within the ambit of this invention. In certain cases the term "epi" is used to distinguish the stereoisomer being of opposite configuration to the natural compound at one specific asymmetrical carbon atom.

Some examples of specific preferred compounds of this inventions are found in the following list of preferred com-

pound,

4a-hydroxy-4"-epiacetylaminoavermectin B_1

4a-hydroxy-4"-epiacetylamino-22,23-dihydroavemectin B_1

4a-acetoxy-4"-epiacetylaminoavemectin B_1

4a-benzoyloxy-4"-epiacetylaminoavermectin B_1

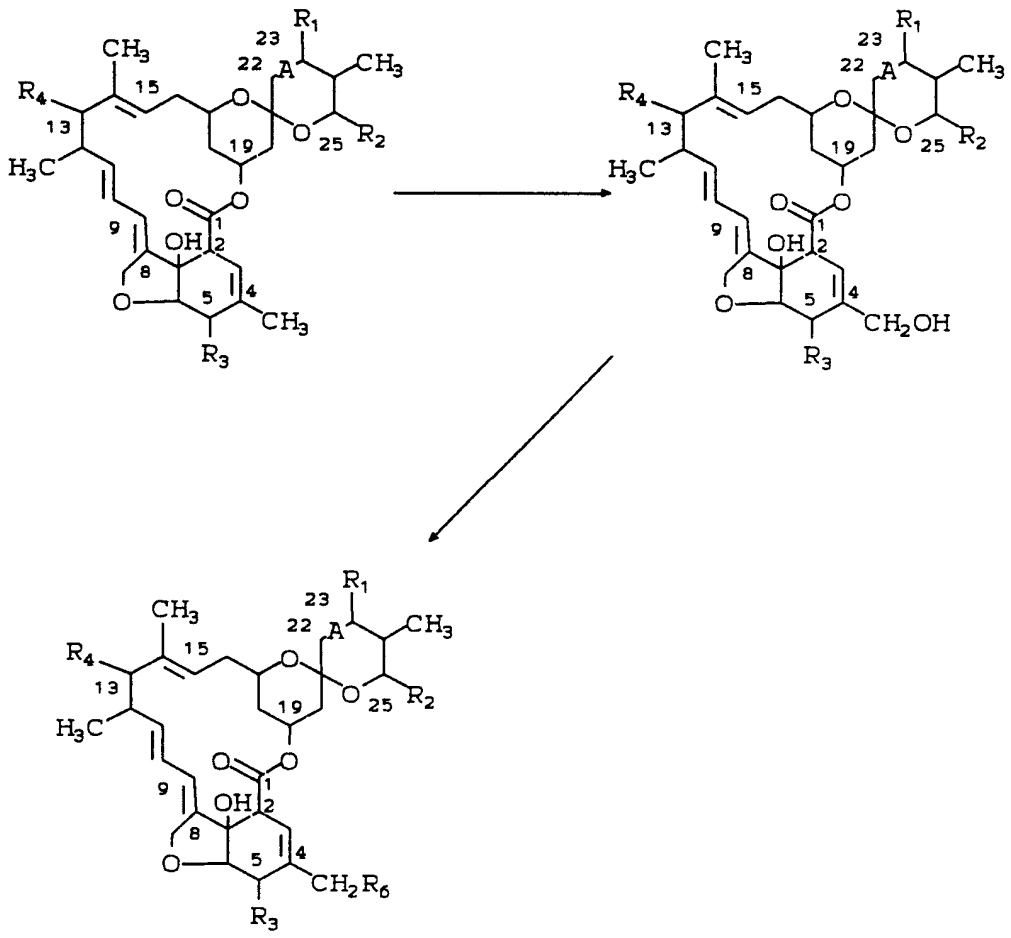
4a-methoxyethoxymethoxy-4"-epiacetylaminoavermectin B_1

4"-epi-N-acetyl-N-methylamino-4a-hydroxyavemectin B_1

4"epi-N-acetyl-N-methylamino-4a-methoxyethoxymethoxyavermectin B_1

4a-methoxyethoxymethoxy-4"-epiacetylamino-22,23-dihydroavermectin B_1

The compounds of the instant invention are prepared according to the following reaction scheme:



In the foregoing, reaction scheme, R_1 R_2, R_3, R_4 and R_6 are as defined above.

In the first step of the reaction, the 4-methyl group is oxidized to a 4a-hydroxy methyl group. The rection is carried out preferably with selenium dioxide and an alkyl hydroperoxide, such as t-butyl-hydroperoxide. The reaction is carried out in a solvent inert to oxidation and halogenated hydro-carbons such as methylene chloride are preferred. The reaction may be carried out at from -20°C to the reflux temperature of the reaction mixture, although room temperature is preferred The reaction is generally complete in from 4 to 40 hours although the progress of the reaction can be monitored by taking aliquots of the reaction mixture and analyzing for the formation of the oxidized product and disappearance of the starting material. This will determine whether the reaction is completed or not, or if necessary, additional oxidizing reagent can be added to the reaction mixture if it is determined that the reaction has not gone to completion. The products are isolated using techniques known to those skilled in the art.

In the oxidation of the 4a-position care must be taken to avoid reaction at other susceptible positions. In particular hydroxy functions are best protected by preparing the alkanoyl derivatives or the ether protected derivatives such as the silyl derivatives discussed below.

Following the formation of the 4a-hydroxy compound, reactions may be carried out at the 4a-position to prepare the additional 4a-derivative and further reactions may be carried out elsewhere on the molecule. The order of the reactions being carried out is not critical however, one skilled in the art will recognize that certain reactions may occur at more than one position and unwanted by-products may be prepared. At each step in the reaction sequence the use of protecting groups may be neccessary or advisable to avoid unwanted reactions.

The acylated derivatives at the 4a-position can be prepared using acylation techniques known to those skilled in the art. One such technique involves the use of triphenylphosphine in an inert solvent such as a halogenated hydrocarbon in the presence of the appropriate carboxylic acid or carboxylic acid derivatives and dialkylazodicarboxylate, preferably diethylazodicarboxylate. The reaction is carried out generally at room temperature although temperature of from -20°C to the reflux temperature of the reaction mixture are acceptable. The reaction is rapid and generally complete in from 5 to 60 minutes.

The preparation of the methoxyethoxymethoxy dervatives is generally carried out using the appropriate methoxyethoxymethyl chloride reagent where the methyl chloride position of the reagent, in combination with the oxygen of the 4a-hydroxy group, becomes the innermost alkoxy group of the final product. The reaction is carried out in the presence of a reagent to remove the liberated proton from the possibility of further reaction. Generally an amine is used as the reagent to absorb the liberated proton and trisubstituted amines are preferred. Most appropriate for this purpose is N,N,N',N'-tetramethyl-1,8-diaminonaphthalene. The proton absorbing reagent and the starting material are combined in an inert solvent, polar solvents such as acetonitrile are preferred, and the methoxyethoxymethyl chloride is added to the reaction mixture. The reaction is generally carried out at room temperature, preferably about 20°C although temperatures of from -20°C to the reflux temperature of the reaction mixture are acceptable. The reaction is generally complete from 1 to 40 hours. The products are isolated using techniques known to those skilled in the art.

During the reactions at the 4a-position it is necessary to protect other hydroxyl groups in the molecule with a protecting group which may be removed after the reaction is accomplished. Typically, hydroxy groups to be protected are found at positions 5, 7, 13, and 23. Suitable protecting groups include tert-butyldimethylsilyl, tert-butyldiphenylsilyl, phenoxyacetyl, acetyl, and the like. The tert-butyldimethylsilyl group is preferred and is introduced by treating a solution of the alcohol in dimethylformamide (DMF) with an excess of imidazole and a silylating reagent such as tert-butyldimethylsilylchloride, tert-butyldimethylsilyl-trifluoromethanesulfonate, and the like at temperatures ranging from -20°C to 50°C for 1 to 48 hours. The reaction is then worked up and the product is isolated and purified using standard techniques known to those skilled in the art. The protecting group may be removed by treatment with a solution of hydrogen fluoride in a pyridine/tetrahydrofuran solvent mixture. Alternatively, the protecting group may be removed by treatment with a solution of p-toluene-sulfonic acid (0.5-2%) in methanol at 0°C to 25°C for 0.5 to 8 hours. Deprotection with hydrogen fluoride in pyridine/tetrahydrofuran is preferred. In both cases reaction workup and product isolation and purification are by standard techniques well known to those skilled in the art.

An amino substituent may be introduced at position 4″ by reductive amination of a 4″-ketone which is in turn prepared by oxidation of the 4″-hydroxyl group present in the avermectins. During the oxidation of the hydroxyl group at C-4″ it is necessary to protect other secondary hydroxyl groups in the molecule (note that it is not necessary to protect the tertiary hydroxyl present at position 7) as described above. With other secondary hydroxyl groups protected the hydroxyl group at position 4″ can be oxidized by a variety of methods to afford the ketone derivatives necessary for conversion to amino and acylamino analogs. The oxidation of this hydroxyl group can be effected by using a variety of oxidation procedures, including oxidation with dimethylsulfoxide (DMSO) based systems commonly known to those skilled in the art as Swern (or Moffat) oxidations (DMSO-oxalyl-chloride, DMSO-acetic anhydride, DMSO-trifluoroacetic anhydride and the like) as well as oxidations with chromium based reagents (pyridinium chlorochromate and the like), or other methods known to those skilled in the art. The DMSO based oxidations are preferred. The oxidation reagent is generated by treating a solution of DMSO in a non-nucleophilic solvent such as dichloromethane (preferred), chloroform, ether, tetrahydrofuran and the like with an electrophilic activating agent such as oxalyl chloride (preferred), dicyclohexylcarbodiimide (DCC), phosgene, and the like at temperatures ranging from -90°C to -55°C and stirring the

mixture thus formed at this temperature for 10 to 90 minutes. To the oxidizing reagent thus generated is added, at the same temperature, a solution of the alcohol in the solvent used to generate the reagent. The solution is stirred at temperatures ranging from -90°C to -55°C for 10 to 90 minutes then a hindered base such as triethylamine, diisopropylethylamine, and the like is added. The temperature is raised to 0°C to 30°C and the mixture stirred at this temperature for 10 to 90 minutes. The reaction is then worked up using standard techniques known to those skilled in the art and the crude product thus obtained is typically used without further purification.

The 4″-ketone functionality thus generated may be used to introduce amino substituents at position 4″ via a reductive amination reaction. The reductive amination affords an avermectin mixture consisting of both possible stereoisomers at position 4″ (4″-alpha-amino and 4″-beta-amino) which is referred to herein as 4″-amino-avermectin. The reductive amination is accomplished by treating a solution of the ketone in an alcoholic solvent such as methanol, ethanol, and the like with an ammonium salt such as ammonium acetate (preferred), ammonium formate, ammonium benzoate and the like at temperatures ranging from -25°C to 25°C for 15 to 60 minutes then adding sodium cyanoborohydride to the resulting mixture and stirring at temperatures ranging from 0°C to 30°C for 30 to 90 minutes. The reaction is then worked up and the product is isolated and purified using standard techniques known to those skilled in the art. The reaction may be modified by substituting an alkylammonium salt in the place of ammonium acetate in the above procedure to prepare avermectin derivatives substituted with an alkylamino group at the 4″ position. Reaction of the 4″-ketone with ammonium acetate or alkylammonium acetate in methanol followed by addition of sodium cyanoborohydride is preferred.

The amino (or alkylamino) substituted derivatives prepared as described above may be acylated to provide acylamino analogs. The acylation is accomplished by treating a solution of the 4"-amino or 4"-alkylamino analog in a halogenated solvent such as dichloromethane, chloroform or the like, or, preferrably, esters such as ethyl acetate, with one molar equivalent of an acylating agent such as an alkanoyl chloride (preferred), alkanoyl bromide, alkanoic acid in combination with dicyclohexylcarbodiimide, and the like in the presence of a base such as triethylamine, pyridine and the like with or without the addition of a nucleophilic catalyst such as dimethylaminopyridine at temperatures ranging from -10°C to 35°C for 15 minutes to 24 hours. The reaction is then worked up and the product is isolated and purified using standard techniques known to those skilled in the art. Note that it is not necessary to protect secondary alcohols in the molecule during the acylation reaction as the amino functionality is sufficiently more reactive that acylation occurs selectively at nitrogen.

The instant compounds of this invention are unexpectedly potent antiparasitic agents against endo and ecto parasites, particularly helminths and arthropods, which cause numerous parasitic diseases in humans, animals, and plants.

Parasitic diseases may be caused by either endoparasites or ectoparasites. Endoparasites are those parasites which live inside the body of the host, either within an organ (such as the stomach, lungs, heart, intestines, etc.) or simply under the skin. Ectoparasites are those parasites which live on the outer surface of the host but still draw nutrients from the host.

The endoparasitic diseases generally referred to as helminthiasis are due to infection of the host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious worldwide economic problem due to infection of domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats, and poultry. Many of these infections are caused by the group of worms described as nematodes which cause diseases in various species of animals throughout the world. These diseases are frequently serious and can result in the death of the infected animal. The most common genera of nematodes infecting the animals referred to above are Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia, Ascaris, Bunostomum, Oesophagostomum, Chabertia, Trichuris, Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris, and Parascaris. Many parasites are species specific (infect only one host) and most also have a preferred site of infection within the animal. Thus Haemonchus and Ostertagia primarily infect the stomach while Nematodirus and Cooperia mostly attack the intestines. Other parasites prefer to reside in the heart, eyes, lungs, blood vessels, and the like while still others are subcutaneous parasites. Helminthiasis can lead to weakness, weight loss, anemia, intestinal damage, malnutrition, and damage to other organs. If left untreated these diseases can result in the death of the animal.

Infections by ectoparasitic arthropods such as ticks, mites, lice, stable flies, hornflies, horseflies, screwworm flies, warble flies, heelflies, deerflies, blowflies, fleas, and the like are also a serious problem. Infection by these parasites results in loss of blood, skin lesions, and can interfere with normal eating habits thus causing weight loss. These infections can also result in transmission of serious diseases such as encephalitis, anaplasmosis, swine pox, and the like which can be fatal.

Animals may be infected by several species of parasite at the same time since infection by one parasite may weaken the animal and make it more susceptible to infection by a second species of parasite. Thus a compound with a broad spectrum of activity is particularly advantageous in the treatment of these diseases. The compounds of this invention have unexpectedly high activity against these parasites, and in addition are also active against Dirofilaria in dogs, Nematospiroides and Syphacia in rodents, biting insects, and migrating diperous larvae such as Hypoderma sp. in cattle, and Gasterophilus in horses.

The instant compounds are also useful against endo and ecto parasites which cause parasitic diseases in humans. Examples of such endoparasites which infect man include gastro-intestinal parasites of the genera Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris, Enterobius, and the like. Other endoparasites which infect man are found in the blood or in other organs. Examples of such parasites are the filarial worms Wucheria, Brugia, Onchocerca, and the like as well as extra-intestinal stages of the intestinal worms Strongyloides and Trichinella. Ectoparasites which parasitize man include arthropods such as ticks, fleas, mites, lice, and the like and, as with domestic animals, infections by these parasites can result in transmission of serious and even fatal diseases. The instant compounds are active against these endo and ecto parasites and in addition are also active against biting insects and other dipterous pests which annoy humans.

The instant compounds are also useful against common household pests such as Blatella sp. (cockroach), Tineola sp. (clothes moth), Attagenus sp. (carpet beetle), Musca domestica (housefly), Solenopsis Invicta (imported fire ant) little housefly, (Fannia canicularis) and the darkling beetle in poultry operations.

The compounds are furthermore useful against agricultural pests such as aphids (Acyrthiosiphon sp.), locusts, and boll weevils as well as against insect pests which attack stored grains such as Tribolium sp. and against immature stages of insects living on plant tissue. The compounds are also useful as nematodicides for the control of soil nematodes which are important to the agricultural community.

For use as an antiparasitic agent in animals the instant compounds may be administered internally either orally or by injection, or topically as a liquid drench or as a shampoo.

For oral administration, the compounds may be administered in capsule, tablet, or bolus form or alternatively they can be mixed in animal feed. The capsules, tablets, and boluses are comprised of the active ingredient in combination with an appropriate carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate. These unit dosage forms are prepared by intimately mixing the active ingredient with suitable finely-powdered inert ingredients including diluents, fillers, disintegrating agents, and/or binders such that a uniform mixture is obtained. An inert ingredient is one that will not react with the instant compounds and which is non-toxic to the animal being treated. Suitable inert ingredients include starch, lactose, talc, magnesium stearate, vegetable gums and oils, and the like. These formulations may contain a widely variable amount of the active and inactive ingredients depending on numerous factors such as the size and type of the animal species to be treated and the type and severity of the infection. The active ingredient may also be administered as an additive to the feed by simply mixing the compound with the feedstuff or by applying the compound to the surface of the feed. Alternatively the active ingredient may be mixed with an inert carrier and the resulting composition may then either be mixed with the feed or fed directly to the animal. Suitable inert carriers include corn meal, citrus meal, fermentation residues, soya grits, dried grains and the like. The active ingredients are intimately mixed with these inert carriers by grinding, stirring, milling, or tumbling such that the final composition contains from 0.001 to 5% by weight of the active ingredient.

The compounds may alternatively be administered parenterally via injection of a formulation consisting of the active ingredient dissolved in an inert liquid carrier. Injection may be either intramuscular, intraruminal, intratracheal, or subcutaneous. The injectable formulation consists of the active ingredient mixed with an appropriate inert liquid carrier. Acceptable liquid carriers include the vegetable oils such as peanut oil, cotton seed oil, sesame oil and the like as well as organic solvents such as solketal, glycerol formal and the like. As an alternative, aqueous parenteral formulations may also be used. The vegetable oils are the preferred liquid carriers. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.005 to 10% by weight of the active ingredient.

Topical application of the instant compounds is possible through the use of a liquid drench or a shampoo containing the instant compounds as an aqueous solution or suspension. These formulations generally contain a suspending agent such as bentonite and normally will also contain an antifoaming agent. Formulations containing from 0.005 to 10% by weight of the active ingredient are acceptable. Preferred formulations are those containing from 0.01 to 5% by weight of the instant compounds.

The instant compounds are primarily useful as antiparasitic agents for the treatment and/or prevention of helminthiasis in domestic animals such as cattle, sheep, horses, dogs, cats, goats, swine, and poultry. They are also useful in the prevention and treatment of parasitic infections of these animals by ectoparasites such as ticks, mites, lice, fleas and the like. They are also effective in the treatment of parasitic infections of humans. In treating such infections the compounds of this invention may be used individually or in combination with each other or with other unrelated antiparasitic agents. The dosage of the instant compounds required for best results depends on several factors such as the species and size of the animal, the type and severity of the infection, the method of administration and the compound used. Oral administration of the instant compounds at a dose level of from 0.0005 to 10 mg per kg of animal body weight, either in a single dose or in several doses spaced a few days apart, generally gives good results. A single dose of one of the instant compounds normally gives excellent control however repeat doses may be given to combat re-infection or for parasite species which are unusually persistent. The techniques for administering these compounds to animals are known to those skilled in the veterinary field.

The compounds of this invention may also be used to combat agricultural pests which attack crops either in the field or in storage. The compounds are applied for such uses as sprays, dusts, emulsions and the like either to the growing plants or the harvested crops. The techniques for applying these compounds in this manner are known to those skilled in the agricultural arts. The compounds of this invention may also be applied to premeses as a spray, paint or wipe oe they may be added to baits. The techniques for applying these compounds are known to those skilled in environmental pest control.

The following examples are provided in order that this invention might be more fully understood; they are not to be construed as limitative of the invention. The avermectin derivatives prepared in the following examples are generally isolated as amorphous solids rather than crystalline solids. They are characterized analytically using techniques such as nuclear magnetic resonance, mass spectrometry, elemental analysis, and the like. Being amorphous the compounds are not characterized by sharp melting points but the chromatographic and analytical methods employed indicate that they are pure.

General. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and by dipping in an aqueous ceric ammonium molybdate solution followed by heating. Solvents for extraction were reagent grade. Solvents for reactions were dried with 3-Å or 4-Å molecular sieves. All reactions were performed under an inert atmosphere of dry nitrogen in dry glassware. ^{1}H NMR spectra were recorded in deuterochloroform on a Varian XL-300 (299.94 MHz) spectrometer. Chemical shifts are reported in ppm from an internal standard of residual chloroform (7.27 ppm). Selected data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened, om = overlapping multiplet), coupling constants (Hz), and assignments. Assignments were made with the aid of 2D (COSY) data. ^{13}C NMR spectra were recorded in deuterochloroform on a Varian XL-300 (75.4 MHz) spectrometer. Chemical shifts are reported in ppm from the central peak of deuterochloroform (77.0 ppm). Assignments were made with the aid of APT data. Data are reported as follows: chemical shift, assignment. Combustion analyses were obtained from Microlit Laboratories, Inc., Caldwell, New Jersey, or Robertson Laboratory, Inc., Madison, NJ.

EXAMPLE 1

4a-Hydroxy-4″-epiacetylaminoavermectin B_1.

A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 12.0 g (13.1 mmol) of 4″-epiacetylaminoavermectin B_1 in 90 mL of dichloromethane. To the resulting clear solution was added 729 mg (6.57 mmol) of selenium dioxide followed by 5.80 mL (5.22 g, 52.5 mmol) of 90% tert-butylhydroperoxide at room temperature. After 22 h, 1.45 mL (1.30 g, 13 mmol) of 90% tert-butylhydroperoxide was added. The resulting solution was stirred at room temperature for 5 h. The reaction mixture was then concentrated by rotary evaporation and chromatographed (7 cm x 30 cm column, 96:4 dichloromethane:methanol for 4 L, then a gradient in 1.5 L, 0.5% methanol increments to 92:8 dichloromethane:methanol) to provide 6.10 g (50%) of 4a-hydroxy-4″-epiacetylaminoavermectin B_1 as a foam: R_f = 0.27 (93:7 dichloromethane/methanol);

^{1}H NMR δ 5.86 (m, H_9), 5.78-5.63 (om, H_3, H_{10}, H_{11}, H_{22}, NH), 5.55 (dd, J = 9.9, 2.5, H_{23}), 5.38-5.25 (om, H_{19}, $H_{1''}$), 4.95 (m, H_{15}), 4.74 (d, J = 3.2, $H_{1'}$), 4.65 (m, H_{8a}), 4.55 (br d, J = 5.0, H_5), 4.38, (dd, J = 10.0, 3.2, $H_{4''}$), 4.22 (brs, H_{4a}), 4.03 (m, $H_{5''}$), 3.97 (d, J = 6.3, H_6), 3.90 (brs, H_{13}), 3.90-3.72 (om, H_{17}, $H_{5'}$), 3.71-3.50 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.42 (s, OCH_3), 3.35 (s, OCH_3), 3.32 (m, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.70 (brs, 2 x OH), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.07 (s, CH_3CO), 2.05-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.65-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.48 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.15 (d, J = 6.9, 3xH_{12a}), 1.10 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax});
^{13}C NMR δ 173.2 (C_1), 170.9 ((C=O)NH), 140.2, 139.3 (C_4, C_8), 138.1 (C_{11}), 136.3 (C_{22}), 135.1 (C_{14}), 127.7 (C_{23}), 124.7 (C_{10}), 120.7, 119.9, 118.3 (C_3, C_9, C_{15}), 98.6 ($C_{1''}$), 95.8 (C_{21}), 94.9 ($C_{1'}$), 81.9 (C_{13}), 81.0 ($C_{4'}$), 80.6 (C_7), 79.3 ($C_{3'}$), 79.2 (C_6), 74.9 (C_{25}), 73.3 ($C_{3''}$), 68.6, 68.3 (C_{17}, C_{19}), 68.4 (C_{8a}), 67.1, 65.5 (C_5, $C_{5'}$, $C_{5''}$), 64.4 (C_{4a}), 56.6, 56.1 (2xOCH_3), 48.5 ($C_{4''}$), 45.6 (C_2), 40.5 (C_{20}), 39.8 (C_{12}), 36.5 (C_{18}), 35.2 (C_{26}), 34.5 ($C_{2'}$), 34.2 (C_{16}), 31.8 ($C_{2''}$), 30.6 (C_{24}), 27.5 (C_{27}), 23.4 (CH_3C=O), 20.2 (C_{12a}), 18.3 ($C_{6'}$), 17.0 ($C_{6''}$), 16.4 (C_{24a}), 15.1 (C_{14a}), 13.0 (C_{26a}), 12.0 (C_{28}), MS (FAB) 952 (M+Na, 4), 330 (26), 305 (22), 300 (20), 221 (20), 186 (100), 154 (82), 112 (34). Anal. Calcd for $C_{50}H_{75}NO_{15}$: C, 64.57; H, 7.95; N, 1.51. Found: C, 64.53; H, 7.95; N, 1.52.

EXAMPLE 2

4a-Hydroxy-4″-epiacetylamino-22,23-dihydroavermectin B_1.

Using the same procedure as Example 1, 4a-hydroxy-4″-epiacetylamino-22,23-dihydroavermectin B_1 was pre-

pared from 4″-epiacetylamino-22,23-dihydroavermectin B_1: yield 404 mg (40%), isolated as a foam: R_f = 0.27 (96:4 dichloromethane/methanol);

^{1}H NMR δ 5.86 (m, H_9), 5.78-5.63 (om, H_3, H_{10}, H_{11}, NH), 5.38-5.25 (om, H_{19}, $H_{1''}$), 4.95 (m, H_{15}), 4.74 (d, J = 3.2, $H_{1'}$), 4.65 (m, H_{8a}), 4.55 (br d, J = 5.0, H_5), 4.40, (dd, J = 10.0, 3.2, $H_{4''}$), 4.25 (m, H_{4a}), 4.03 (m, $H_{5''}$), 3.92 (d, J = 6.3, H_6), 3.90 (brs, H_{13}), 3.88-3.72 (m, H_{17}), 3.71-3.50 (om, $H_{3'}$, $H_{3''}$, $H_{5'}$), 3.42 (s, OCH_3), 3.35 (s, OCH_3), 3.32 (m, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.70 (brs, 2 x OH), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.07 (s, CH_3CO), 2.05-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.65-1.40 (om, H_{20}, 2xH_{22}, 2xH_{23},.H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.48 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.15 (d, J = 6.9, 3xH_{12a}), 1.10 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax});
^{13}C NMR δ 173.3 (C_1), 170.9 ((C=O)NH), 140.1, 139.3 (C_4, C_8), 138.1 (C_{11}), 135.0 (C_{14}), 124.7 (C_{10}), 120.7, 119.9, 118.3 (C_3, C_9, C_{15}), 98.6 ($C_{1''}$), 97.5 (C_{21}), 94.8 ($C_{1'}$), 81.8 (C_{13}), 81.0 ($C_{4'}$), 80.6 (C_7), 79.3 ($C_{3'}$), 79.1 (C_6), 76.6 (C_{25}), 73.3 ($C_{3''}$), 68.9, 67.2 (C_{17}, C_{19}), 68.5 (C_{8a}), 67.0, 65.7, 65.5 (C_5, $C_{5'}$, $C_{5''}$), 64.5 (C_{4a}), 56.6, 56.1 (2xOCH_3), 48.5 ($C_{4''}$), 45.6 (C_2), 41.2 (C_{20}), 39.7 (C_{12}), 36.9 (C_{18}), 35.7 (C_{22}), 35.4 (C_{26}), 34.5 ($C_{2'}$), 34.1 (C_{16}), 31.8 ($C_{2''}$), 31.2 (C_{24}), 28.1 (C_{27}), 27.3 (C_{23}), 23.5 (CH_3C=O), 20.2 (C_{12a}), 18.3 ($C_{6'}$), 17.5 ($C_{6''}$), 17.1 (C_{24a}), 15.1 (C_{14a}), 12.5 (C_{26a}), 12.1 (C_{28}); MS (FAB) 938 (M+Li, 100). Anal. Calcd for $C_{50}H_{77}NO_{15}$: C, 64.43; H, 8.33; N, 1.50. Found: C, 64.87; H, 8.43; N, 1.43.

EXAMPLE 4

4a-Acetoxy-4"-epiacetylaminoavermectin B_1.

A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 257 mg (276 μmol) of 4a-hydroxy-4"-epiacetylaminoavermectin B_1, 94 mg (359 μmol) of Ph_3P and 21 μl (22 mg, 359 μmol) of acetic acid in 5 mL of dichloromethane. To the resulting clear solution was added 56 μl (62 mg, 359 μmol) of diethyl azodicarboxylate at room temperature over 5 min. The resulting solution was stirred at room temperature for 15 min. The reaction was quenched by the addition of 15 mL of saturated aqueous sodium bicarbonate and poured into a separatory funnel containing 15 mL of dichloromethane. The layers were separated and the aqueous layer was extracted with 2 x 15 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered concentrated and chromatographed (2 cm x 25 cm column, ethyl acetate) to provide 188 mg (70%) of 4a-acetoxy-4"-epiacetylaminoavermectin B_1 as a foam: R_f = 0.25 (ethyl acetate);

^{1}H NMR δ 5.86 (m, H9), 5.78-5.68 (om, H_3, H_{10}, H_{11}, NH), 5.58 (d, J = 9.9, H_{22}), 5.55 (dd, J = 9.9, 2.5, H_{23}), 5.38-5.25 (om, H_{19}, $H_{1''}$), 4.95 (m, H_{15}), 4.80-4.60 (om, $H_{1'}$, 2xH_{8a}, 2xH_{4a}), 4.45 (d, J = 5.0, H_5), 4.42, (dd, J = 10.0, 3.2, $H_{4''}$), 4.03 (m, $H_{5''}$), 3.97 (d, J = 6.3, H_6), 3.90 (brs, H_{13}), 3.90-3.72 (om, H_{17}, $H_{5'}$), 3.71-3.52 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.42 (s, OCH_3), 3.35 (s, OCH_3), 3.32 (m, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.07 (s, CH_3CO), 2.05 (s, CH_3CO), 1.95-1.85 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.65-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.48 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.15 (d, J = 6.9, 3xH_{12a}), 1.10 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax});
^{13}C NMR δ 173.2 (C_1), 170.9, 170.8 (CH_3CONH, CH_3CO_2), 139.3, 136.5 (C_4, C_8), 138.3 (C_{11}), 136.3 (C_{22}), 135.1 (C_{14}), 127.7 (C_{23}), 124.7 (C_{10}), 121.6, 120.7, 118.3 (C_3, C_9, C_{15}), 98.6 ($C_{1''}$), 95.8 (C_{21}), 94.9 ($C_{1'}$), 81.9 (C_{13}), 81.0 ($C_{4'}$), 80.5 (C_7), 79.3 ($C_{3'}$), 79.0 (C_6), 74.9 (C_{25}), 73.3 ($C_{3''}$), 68.7, 68.3 (C_{17}, C_{19}), 68.5 (C_{8a}), 67.1, 65.5, 64.7 (C_5, $C_{5'}$, $C_{5''}$), 64.4 (C_{4a}), 56.6, 56.1 (2xOCH_3), 48.4 ($C_{4''}$), 45.6 (C_2), 40.5 (C_{20}), 39.8 (C_{12}), 36.6 (C_{18}), 35.1 (C_{26}), 34.5 ($C_{2'}$), 34.2 (C_{16}), 31.9 ($C_{2''}$), 30.6 (C_{24}), 27.5 (C_{27}), 23.5 (CH_3CONH), 21.0 (CH_3CO_2), 20.2 (C_{12a}), 18.3 ($C_{6'}$), 17.1 ($C_{6''}$), 16.4 (C_{24a}), 15.1 (C_{14a}) 13.0 (C_{26a}), 12.0 (C_{28}); MS (FAB) 972 (M+H, 100). Anal. Calcd for $C_{52}H_{77}NO_{16}$: C, 64.24; H, 7.98; N, 1.44. Found: C, 64.58; H, 7.86; N, 1.08.

EXAMPLE 5

4a-Benzoyloxy-4″-epiacetylaminoavermectin B_1.

A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 402 mg (432 μmol) of 4a-hydroxy-4″-epiacetylaminoavermectin B_1, 142 mg (540 μmol) of Ph_3P and 132 mg (1.08 mmol) of benzoic acid in 4 mL of dichloromethane. To the resulting clear solution was added 85 μl (94 mg, 540 μmol) of diethyl azodicarboxylate at room temperature over 5 min. The resulting solution was stirred at room temperature for 15 min. The reaction was quenched by the addition of 15 mL of saturated aqueous sodium bicarbonate and poured into a separatory funnel containing 15 mL of dichloromethane. The layers were separated and the aqueous layer was extracted with 2 x 15 mL of dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered concentrated and

chromatographed (2 cm x 25 cm column, 97:3 dichloromethane:methanol) to provide 374 mg (84%) of 4a-benzoyl-4″-epiacetylaminoavermectin B_1 as a foam: Rf = 0.25 (97:3 dichloromethane: methanol);

^{1}H NMR δ 8.05 (m, 2xarom. H), 7.55 (m, arom. H), 7.40 (m, 2xarom. H), 5.86 (m, H_9), 5.81 (m, H_3), 5.78-5.68 (om, H_{10}, H_{11}, NH), 5.58 (d, J = 9.9, H_{22}), 5.52 (dd, J = 9.9, 2.5, H_{23}), 5.45-5.30 (om, H_{19}, $H_{1''}$), 5.05-4.88 (m, 2xH_{4a}, H_{15}), 4.74 (d, J = 3.1, $H_{1'}$), 4.68 (m, 2xH_{8a}), 4.54 (d, J = 5.0, H_5), 4.40, (dd, J = 10.0, 3.2, $H_{4''}$), 4.03 (m, $H_{5''}$), 4.00 (d, J = 6.3, H_6), 3.90 (brs, H_{13}), 3.90-3.68 (om, H_{17}, $H_{5'}$), 3.71-3.52 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.41 (s, OCH_3), 3.37 (om, OCH_3, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.75 (m, OH), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.04 (s, CH_3CO), 1.95-1.85 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.65-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.47 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.15 (d, J = 6.9, 3xH_{12a}), 1.10 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax});
^{13}c NMR δ 173.2 (C_1), 170.7 (CH_3CONH), 166.3 ($ArCO_2$), 139.3 (C_8), 138.2 (C_{11}), 136.7 (C_4), 136.3 (C_{22}), 135.1 (C_{14}), 133.1 (arom), 129.9 (3xarom), 128.4 (2xarom), 127.7 (C_{23}), 124.7 (C_{10}), 121.5, 120.7, 118.3 (C_3, C_9, C_{15}), 98.7 ($C_{1''}$), 95.8 (C_{21}), 94.9 ($C_{1'}$), 81.9 (C_{13}), 81.0 ($C_{4'}$), 80.5 (C_7), 79.3 ($C_{3'}$), 79.0 (C_6), 74.9 (C_{25}), 73.3 ($C_{3''}$), 68.6, 68.3 (C_{17}, C_{19}), 68.5 (C_{8a}), 67.1, 65.5, 64.4 (C_5, $C_{5'}$, $C_{5''}$), 64.8 (C_{4a}), 56.6, 56.1 (2xOCH_3), 48.4 ($C_{4''}$), 45.6 (C_2), 40.4 (C_{20}), 39.8 (C_{12}), 36.6 (C_{18}), 35.1 (C_{26}), 34.5 ($C_{2'}$), 34.3 (C_{16}), 31.9 ($C_{2''}$), 30.6 (C_{24}), 27.5 (C_{27}), 23.5 (CH_3CONH), 20.2 (C_{12a}), 18.3 ($C_{6'}$), 17.1 ($C_{6''}$), 16.4 (C_{24a}), 15.1 (C_{14a}), 13.0 (C_{26a}), 12.0 (C_{28}); MS (FAB) 1040 (M+Li, 100). Anal. Calcd for $C_{57}H_{79}NO_{16}$: C, 66.20; H, 7.70; N, 1.35. Found: C, 66.40; H, 7.68; N, 1.42.

EXAMPLE 7

4a-Methoxyethoxymethoxy-4"-epiacetylaminoavermectin B_1:

(A) 4a-tert-Butyldimethylsilyloxy-4"-epiacetylaminoavermectin B_1. A 100-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 4.58 g (4.93 mmol) of 4a-hydroxy-4"-epiacetylaminoavermectin B_1 (see Example 1) in 27 mL of dichloromethane. To the clear solution was added 180 mg (1.48 mmol) of N,N-dimethylaminopyridine and 1.10 mL (799 mg, 7.88 mmol) of triethylamine followed by 965 mg (6.40 mmol) of t-butylchlorodimethylsilane. After stirring at 20°C for 17 h, 390 mg (2.58 mmol) of t-butylchlorodimethylsilane and 345 μl (250 mg, 2.48 mmol) of triethylamine were added. After stirring for another 5 h, the reaction mixture was added to 50 mL of water. The layers were separated and the aqueous phase was extracted with 5 x 40 mL of dichloromethane. The organic layers were combined, washed with 200 mL of saturated aqueous sodium bicarbonate, 2 x 100 mL of water, and 150 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (7 cm x 30 cm column, 96.5:3.5 dichloromethane:methanol) to afford 4.20 g (82%) of the silyl ether as a foam: R_f = 0.16 (96.5:3.5 dichloromethane:methanol);

^{1}H NMR δ 5.86 (m, H_9), 5.78-5.65 (om, H_3, H_{10}, H_{11}, H_{22}), 5.55 (om, H_{23}, NH), 5.45-5.30 (om, H_{19}, $H_{1''}$), 4.95 (m, H_{15}), 4.74 (d, J = 3.1, $H_{1'}$), 4.68 (m, 2xH_{8a}), 4.50-4.30 (om, H_5, 2xH_{4a}, $H_{4''}$), 4.10-4.00 (m, $H_{5''}$, 7-OH), 3.98 (d, J = 6.3, H_6), 3.90 (brs, H_{13}), 3.90-3.68 (om, H_{17}, $H_{5'}$), 3.71-3.52 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.41 (s, OCH_3), 3.37 (s, OCH_3), 3.32 (m, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.75 (m, 5-OH), 2.50 (m, H_{12}), 2.32-2.12 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.03 (s, CH_3CO), 2.08-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.68-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.46 (s, 3xH_{14a}), 1.22 (d, J = 6.2, 3x$H_{6'}$), 1.15 (d, J = 6.9, 3xH_{12a}), 1.10 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax}, $SiC(CH_3)_3$), 0.05 (s, $Si(CH_3)_2$); MS (FAB) 1066 (M+Na, 100). Anal. Calcd for $C_{56}H_{89}NO_{15}Si$: C, 64.40; H, 8.59; N, 1.34. Found: C, 64.67; H, 8.60; N, 1.22.

(B) 4a-tert-Butyldimethylsilyloxy-5-O-phenoxyacetyl-4"-epiacetylaminoaver-mectin B_1. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 4.20 g (4.02 mmol) of 4a-tert-butyldimethyl silyloxy-4"-epiacetylaminoavermectin B_1 in 40 mL of dichloromethane. To the clear solution was added 492 mg (4.02 mmol) of N,N-dimethylaminopyridine and 3.3 mL (3.2 g, 41 mmol) of pyridine followed by 700 μl (865 mg, 5.07 mmol) of phenoxyacetyl chloride. After stirring at 20°C for 40 min, 50 mL of 1.0 M aqueous sodium hydrogen sulfate was added. The resulting mixture was stirred for 10 min, then transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted with 4 x 40 mL of dichloromethane. The organic layers were combined, washed with 2 x 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (5 cm x 23 cm column, 97:3 dichloromethane:methanol) to afford 4.60 g (97%) of the silyl ether-ester as a foam: R_f = 0.23 (97:3 dichloromethane:methanol);

^{1}H NMR δ 7.30 (m, arom 2xH), 7.15-6.90 (om, arom 3xH), 5.86 (om, H_3, H_9), 5.82-5.70 (om, H_5, H_{10}, H_{11}, H_{22}), 5.60 (om, H_{23}, NH), 5.50-5.38 (om, H_{19}, $H_{1''}$), 5.00 (m, H_{15}), 4.80 (d, J = 3.1, $H_{1'}$), 4.70 (s, OCH_2Ar), 4.65 (m,

2xH_{8a}), 4.45 (dd J = 10.0, 3.2, $H_{4''}$), 4.15 (d, J = 6.3, H_6), 4.10 (brs, H_{4a}), 4.05 (m, $H_{5''}$), 3.97 (s, 7-OH), 3.90-3.70 (om, H_{17}, $H_{5'}$), 3.68-3.45 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.41 (s, OCH_3), 3.37 (om, OCH_3, H_2), 3.18 (t, J = 9.0, $H_{4'}$), 2.50 (m, H_{12}), 2.32-2.12 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.04 (s, CH_3CO), 2.08-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.75 (m, H_{18eq}), 1.68-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.48 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.13 (d, J = 6.9, 3xH_{12a}), 1.11 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax}, $SiC(CH_3)_3$), 0.05 (s, $Si(CH_3)_2$);

^{13}C NMR δ 173.0 (C_1), 170.7 (CH_3CONH), 169.8 ($ArCO_2$), 147.2 (aromC), 139.2 (C_8), 138.1 (C_{11}), 136.4 (C_4), 136.3 (C_{22}), 135.1 (C_{14}), 129.5 (2xaromC), 127.8 (C_{23}), 124.8 (C_{10}), 121.7 (aromC), 121.2, 120.8, 118.3 (C_3, C_9, C_{15}), 114.6 (2xaromC), 98.7 ($C_{1''}$), 95.8 (C_{21}), 94.9 ($C_{1'}$), 81.9 (C_{13}), 81.0 ($C_{4'}$), 80.9 (C_7), 79.3 ($C_{3'}$), 77.2 (C_6), 74.9 (C_{25}), 73.3 ($C_{3''}$), 68.5, 68.3 (C_{17}, C_{19}), 68.4 (C_{8a}), 67.9, 67.1, 65.5 (C_5, $C_{5'}$, $C_{5''}$), 64.0 (C_{4a}), 63.1 (OCH_2Ar), 56.7, 56.1 (2xOCH_3), 48.4 ($C_{4''}$), 45.5 (C_2), 40.4 (C_{20}), 39.8 (C_{12}), 36.6 (C_{18}), 35.1 (C_{26}), 34.5 ($C_{2'}$), 34.2 (C_{16}), 31.9 ($C_{2''}$), 30.6 (C_{24}), 27.5 (C_{27}), 25.9 ($C(CH_3)_3$), 23.5 (CH_3CONH), 20.2 (C_{12a}), 18.3 ($C_{6'}$), 17.1 ($C_{6''}$), 16.4 (C_{24a}), 15.1 (C_{14a}), 13.0 (C_{26a}), 12.1 (C_{28}); MS (FAB) 1184 (M+Li, 100). Anal. Calcd for $C_{64}H_{95}NO_{17}Si$: C, 65.23; H, 8.12; N, 1.19. Found: C, 65.48; H, 8.38; N, 1.11.

(C) 4a-Hydroxy-5-O-phenoxyacetyl-4''-epiacetylaminoavermectin B_1. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 4.40 g (3.73 mmol) of 4a-tert-butyldimethylsilyloxy-5-O-phenoxyacetyl-4''-epiacetylaminoavermectin B_1 in 36 mL of methanol. The clear solution was cooled to 0°C and 35.5 mL of 2% p-toluenesulfonic acid in methanol was added dropwise. After stirring at 0°C for 2 h, 70 mL of saturated aqueous sodium bicarbonate was added, followed by 50 mL of water. The resulting mixture was transferred to a separatory funnel and extracted with 4 x 70 mL of dichloromethane. The organic layers were combined, washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (7 cm x 28 cm column, 96.25:3.75 dichloromethane:methanol) to afford 3.07 g (77%) of the alcohol as a foam: R_f = 0.20 (94:6 dichloromethane:methanol);

^{1}H NMR δ 7.28 (d, J = 7.0, arom 2xH), 6.98 (t, J = 7.0, aromH), 6.90 (d, J = 7.0, 2xaromH), 5.91 (brs, H_3), 5.86 (m, H_9), 5.80-5.68 (om, H_5, H_{10}, H_{11}, H_{22}), 5.55 (om, H_{23}, NH), 5.45-5.37 (om, H_{19}, $H_{1''}$), 4.98 (m, H_{15}), 4.75 (d, J = 2.3, $H_{1'}$), 4.70 (s, OCH_2Ar), 4.60 (m, 2xH_{8a}), 4.42 (dm J = 10.0, $H_{4''}$), 4.16 (d, J = 6.1, H_6), 4.10 (om, H_{4a}, $H_{5''}$), 3.92 (brs, H_{13}), 3.90-3.78 (om, H_{17}, $H_{5'}$), 3.72-3.55 (om, $H_{3'}$, $H_{3''}$), 3.45 (d, J = 10, H_{25}), 3.41 (s, OCH_3), 3.37 (om, OCH_3, H_2), 3.19 (t, J = 9.0, $H_{4'}$), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.04 (s, CH_3CO), 2.08-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.78 (m, H_{18eq}), 1.68-1.40 (om, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.48 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.13 (d, J = 6.9, 3xH_{12a}), 1.11 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax}); MS (FAB) 1086 (M+Na, 100). Anal. Calcd for $C_{58}H_{81}NO_{17}$: C, 65.46; H, 7.67; N, 1.32. Found: C, 65.68; H, 7.85; N, 0.94.

(D) 4a-Methoxyethoxymethoxy-4''-epiacetylaminoavermectin B_1. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 3.07 g (2.89 mmol) of 4a-hydroxy-5-O-phenoxyacetyl-4''-epiacetylaminoavermectin B_1 in 20 mL of acetonitrile. The clear solution was cooled to 0°C and 3.40 g (15.9 mmol) of N,N,N',N'-tetramethyl-1,8-naphthalenediamine (proton sponge) was added in one portion, followed by a dropwise addition of 1.32 mL (1.44 g, 11.5 mmol) of 2-methoxyethoxymethyl chloride (MEM chloride). After stirring at 0°C for 6 min, the reaction mixture was warmed to room temperature and stirred overnight. The amine-hydrochloride salt slowly precipitated from solution. After 14 h, 75 mL of saturated aqueous sodium bicarbonate was added, followed by 50 mL of water. The resulting mixture was transferred to a separatory funnel and extracted with 6 x 30 mL of ethyl acetate. The organic layers were combined, washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (7 cm x 27 cm column, 96.75:3.25 dichloromethane:methanol) to afford 3.54 g (100+%) of the ether as a foam. This material was deprotected without further purification: R_f = 0.33 (95:5 dichloromethane:methanol).

A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 3.54 g (~2.89 mmol) of 4a-methoxyethoxymethoxy-5-O-phenoxyacetyl-4''-epiacetylaminoavermectin B_1 in 90 mL of dry tetrahydrofuran. The clear solution was cooled to -20°C and 23 mL (1.0 M in tetrahydrofuran, 23 mmol) of lithium tri-sec-butylborohydride (L-selectride) was added dropwise over 5 min via syringe. The reaction mixture was placed in a -20°C freezer for 15 h. The reaction was stopped by the addition of 50 mL of water. The resulting mixture was transferred to a separatory funnel and extracted with 7 x 30 mL of dichloromethane. The organic layers were combined, washed with 2 x 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (7 cm x 27 cm column, 95.5:4.5

dichloromethane:methanol) to afford 1.11 g (38%) of the desired product as a foam and 1.43 g of mixed fractions. Chromatography (5 cm x 27 cm column, 95.5:4.5 dichloromethane:methanol) of the mixed fractions provided an additional 0.63 g (21%) of material for a total of 1.74 g (59%). R_f = 0.13 (95.5:4.5 dichloromethane:methanol).

^{1}H NMR δ 5.85 (m, H_9), 5.78-5.68 (om, H_{10}, H_{11}, H_{22}, NH), 5.55 (om, H_3, H_{23}), 5.45-5.35 (om, H_{19}, $H_{1''}$), 4.98 (m, H_{15}), 4.80-4.75 (om, 2xH_{8a}, $H_{1'}$, OCH_2O), 4.52 (brt, J = ~5, H_5), 4.42 (dm J = 10.0, $H_{4''}$), 4.28 (brd, J = ~10, H_{4a}), 4.12 (brd, J = ~10, H_{4a}), 4.08 (s, 7-OH), 4.05 (m, $H_{5''}$), 3.98 (d, J = 6.1, H_6), 3.92 (brs, H_{13}), 3.90-3.78 (om, H_{17}, $H_{5'}$), 3.75-3.50 (om, $H_{3'}$, $H_{3''}$, OCH_2CH_2O), 3.45 (d, J = 10, H_{25}), 3.40 (s, OCH_3), 3.35 (s, OCH_3), 3.35 (om, OCH_3, H_2), 3.19 (t, J = 9.0, $H_{4'}$), 2.85 (d, J = 5, 5-OH), 2.50 (m, H_{12}), 2.32-2.15 (om, 2xH_{16}, H_{24}, $H_{2'eq}$), 2.04 (s, CH_3CO), 2.08-1.95 (om, H_{20eq}, $H_{2''eq}$), 1.78-1.40 (om, H_{18eq}, H_{20}, H_{26}, 2xH_{27}, $H_{2'}$, $H_{2''}$), 1.45 (s, 3xH_{14a}), 1.21 (d, J = 6.2, 3x$H_{6'}$), 1.13 (d, J = 6.9, 3xH_{12a}), 1.11 (d, J = 6.6, 3x$H_{6''}$), 0.95-0.85 (om, 3xH_{24a}, 3xH_{26a}, 3xH_{28}, H_{18ax}); MS (FAB) 1040 (M+Na, 100), 1018 (M+H, 40).

EXAMPLE 14

4"-epi-N-Acetyl-N-methylamino-4a-hydroxyavermectin B_1.

(A) 4"-epi-N-Acetyl-N-methylaminoavermectin B_1. A 250-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 5.00 g (5.54 mmol) of 4"-epi-N-methylaminoavermectin B_1 in 50 mL of ethyl acetate. To the resulting clear solution was added 800 μL (873 mg, 8.46 mmol) of acetic anhydride at room temperature. After stirring for 18 h, 10 mL of saturated aqueous sodium bicarbonate was added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was washed with 30 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, concentrated by rotary evaporation and chromatographed (4 cm x 20 cm column, 97:3 dichloromethane:methanol) to provide 5.13 g (98%) of 4"-epi-N-acetyl-N-methylaminoavermectin B_1 as a foam: R_f=0.35 (93:7 dichloromethane/methanol).

(B) Using the same procedure as Example 1, 4"-epi-N-acetylamino-N-methyl-4a-hydroxyavermectin B_1 was prepared from 4"-epi-N-acetylamino-N-methylavermectin B_1: yield 404 mg (33%), isolated as a foam: R_f = 0.19 (94:6 dichloromethane/methanol); MS (FAB) 966 (M+Na, 80), 344 (90), 312 (100), 221 (95).

EXAMPLE 19

13-O-Methoxyethoxymethyl-4a-methoxyethoxymethoxy-22,23-dihydroavermectin B_1 aglycone

(A) 4a-tert-Butyldimethylsiloxy-5-O-tert-butyldimethylsilyl-13-O-methoxyethoxymethyl-22,23-dihy droavermectin B_1 aglycone.

A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 400 mg (567 μmol) of 13-O-methoxyethoxymethyl-4a-hydroxy-22,23- dihydroavermectin B_1 aglycone (Example 3) in 4 mL of N,N-dimethylformamide. To the clear solution was added 231 mg (3.40 mmol) of imidazole and 256 mg (1.70 mmol) of tert-butylchlorodimethylsilane. After stirring at 20°C for 3.75 h, the reaction mixture was quenched by the addition of 10 mL of water followed by 10 mL of ethyl acetate. The layers were separated and the aqueous phase was extracted with 4 x 10 mL of ethyl acetate. The organic layers were combined, washed with 50 mL of water, dried over sodium sulfate, filtered, concentrated and chromatographed (4 cm x 27 cm column, 8:1 hexane:ethyl acetate) to afford 468 mg (88%) of 4a-tert-butyldimethylsiloxy-5-O-tert-butyldimethylsilyl-13-O-methoxyethoxymethyl-2 2,23-dihydroavermectin B_1 aglycone as a foam: R_f = 0.42 (4:1 hexane:ethyl acetate).

(B) 5-O-tert-Butyldimethylsilyl-4a-hydroxy-13-O-methoxyethoxymethyl-22,23-dihydroavermectin B_1 aglycone

A 50-mL polypropylene vial fitted with a magnetic stirring bar was charged with 468 mg (0.510 mmol) of 4a-tert-butyldimethylsiloxy-5-O-tertbutyldimethylsilyl-13-O-methoxyethoxymethyl-22,23-dihy droavermectin B_1 aglycone in 25 mL of tetrahydrofuran. The clear solution was cooled to 0°C and 1.7 mL of hydrogen fluoride-pyridine solution (the solution consists of 25 g of commercial hydrogen fluoride-pyridine diluted with 27.5 mL of tetrahydrofuran and 12.5 mL of pyridine) was added dropwise. After warming to room temperature and stirring for 3.7 h, 5 mL of pyridine followed by 15 mL of saturated aqueous potassium carbonate was added. The resulting mixture was transferred to a separatory funnel and extracted with 4 x 15 mL of ethyl acetate. The organic layers were combined and washed with 3 x 20 mL of saturated aqueous potassium carbonate. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (4 cm x 27 cm column, 3:1 hexane:ethyl acetate) to afford 404 mg (98%) of 5-O-tert-butyldimethyls-

ilyl-4a-hydroxy-13-O-methoxyeth oxymethyl-22,23-dihydroavermectin B_1 aglycone as a foam: R_f = 0.35 (3:1 hexane:acetone).

(C) 5-O-tert-Butyldimethylsilyl-4a- methoxyethoxymethoxy-13-O-methoxyethoxymethyl-22,23-dihydroavermectin B_1 aglycone

A 25-mL round-bottom flask fitted with a magnetic stirring bar, septum and nitrogen inlet was charged with 404 mg (0.502 mmol) of 5-O-tert-butyldimethylsilyl-4a-hydroxy-13-O-methoxyethoxymethyl -22,23-dihydroavermectin B_1 aglycone in 8 mL of acetonitrile. The clear solution was cooled to 0°C and 539 mg (2.51 mmol) of N,N,N′,N′-tetramethyl-1,8-naphthalenediamine was added in one portion, followed by a dropwise addition of 188 μL (205 mg, 1.51 mmol) of methoxyethoxymethyl chloride (MEM chloride). After stirring at 0°C for 3 min, the reaction mixture was warmed to room temperature and stirred. The amine-hydrochloride salt slowly precipitated from solution. After 20 h, 10 mL of saturated aqueous sodium bicarbonate was added, followed by 5 mL of water. The resulting mixture was transferred to a separatory funnel and extracted with 6 x 10 mL of ethyl acetate. The organic layers were combined, washed with 30 mL of saturated aqueous sodium bicarbonate, 30 mL of 1 N sodium hydrogen sulfate and 30 mL of saturated aqueous sodium chloride. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (4 cm x 30 cm column, 75:25 hexane:acetone) to afford 288 mg (64%) of 5-O-tertbutyldimethylsilyl-4a-methoxyethoxymethoxy-13-O-methoxyethoxymethyl-22,23-dihydroavermectin B_1 aglycone as a foam: R_f = 0.44 (2:1 hexane:acetone).

(D) 13-O-Methoxyethoxymethyl-4a-methoxyethoxymethoxy-22,23-dihydroavermectin B_1 aglycone

A 20-mL polypropylene vial fitted with a magnetic stirring bar was charged with 288 mg (322 μmol) of 5-O-tert-butyldimethylsilyl-4a-methoxyethoxymethoxy-13-O-methoxyethoxymethyl-22,23-dihydroavermectin B_1 aglycone in 6 mL of tetrahydrofuran. The clear solution was cooled to 0°C and 1.6 mL of hydrogen fluoride-pyridine solution (the solution consists of 25 g of commercial hydrogen fluoridepyridine diluted with 27.5 mL of tetrahydrofuran and 12.5 mL of pyridine) was added dropwise. After warming to room temperature and stirring for 16 h, 5 mL of pyridine followed by 5 mL of saturated aqueous potassium carbonate was added. The resulting mixture was transferred to a separatory funnel and extracted with 5 x 15 mL of ethyl acetate. The organic layers were combined and washed with 4 x 10 mL of saturated aqueous potassium carbonate. The organic phase was then dried over sodium sulfate, filtered, concentrated and chromatographed (3 cm x 23 cm, 1:3 hexane:ethyl acetate) to afford 220 mg (88%) of 13-O-methoxyethoxymethyl-4a-methoxyethoxymethoxy-22,23 -dihydroavermectin B_1 aglycone as a foam: R_f = 0.23 (1:3 hexane:ethyl acetate); MS (FAB) 786 (M+Li, 100), 686 (20).

EXAMPLE 20

4"-epi-N-Acetyl-N-methylamino-4a-methoxyethoxymethoxyavermectin B_1

Using the same procedures (steps A-D) provided for Example 19, 170 mg of 4"epi-N-acetyl-N-methylamino-4a-methoxyethoxymethoxyav ermectin B_1 was prepared from 295 mg of 4"-epi-N-acetyl-N-methylamino-4a-hydroxyavermectin (Example 14). Data for 4"epi-N-acetyl-N-methylamino-4a-methoxyethoxymethoxyavermectin B_1: R_f = 0.23 (96:4 dichloromethane:methanol); MS (FAB) 1038 (M+Li, 85), 939 (50), 200 (100), 161 (62).

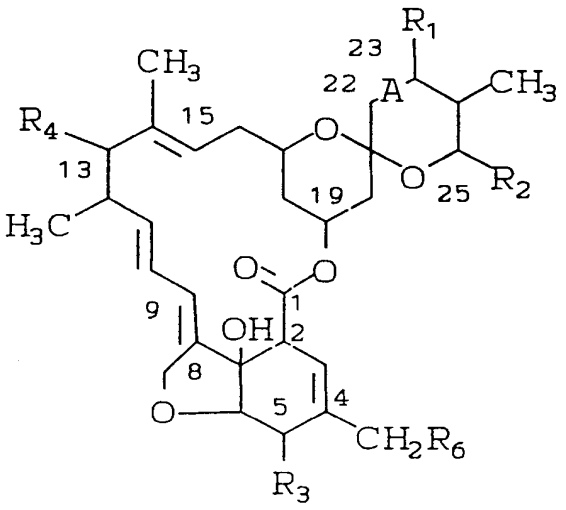
EXAMPLE 24

4a-Methoxyethoxymethoxy-4"-epiacetylamino-22, 23-dihydroavermectin B_1

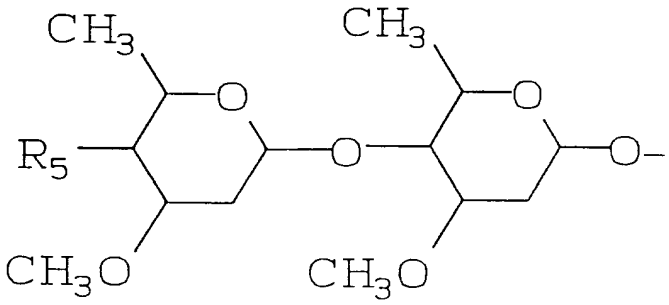
A 100-mL round-bottom flask fitted with a magnetic stirring bar, septum and gas inlet was charged with 1.00 g (0.982 mmol) of 4a-methoxyethoxymethoxy-4"-epiacetylaminaavermectin B_1 (see Example 7) in 12 mL of toluene. To the clear solution was added 273 mg (0.295 mmol) of tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst). The system was evacuated (20 torr) and purged with nitrogen three times, followed by hydrogen three times. Finally, the system was put under a static balloon of hydrogen and stirred at room temperature. After stirring for 24 h, the reaction mixture was flushed with nitrogen, concentrated and chromatographed (6 cm x 32 cm column, 96:4 dichloromethane:methanol) to afford 1.00 g (99%) of the the impure product. Purification in two batches by preparative HPLC (2 cm x 50 cm Whatman Partisil-10 ODS column, 254 nm, 82:18 methanol:water, 10 mL/min) provided pure 4a-methoxyethoxymethoxy-4"-epiacetylamino-22,23-dihydroavermectin B_1: R_f = 0.16 (96.5:3.5 dichloromethane:methanol); MS (FAB) 1027 (M+Li, 100).

Claims

1. A compound having the formula



A is a 22,23-single bond or double bond and R_1 is hydrogen;
R_2 is isopropyl or sec-butyl;
R_3 is hydroxy;
R_4 is

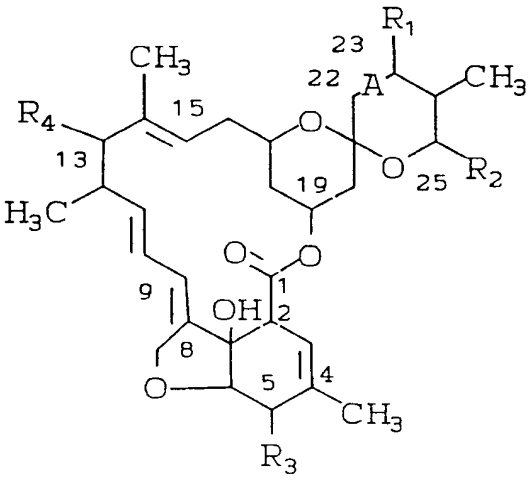


where
R_5 is N-acetyl amino or N-methyl-N-acetyl amino; and
R_6 is hydroxy, acetoxy, benzoyloxy, nicotinoyloxy, or methoxy ethoxy methoxy.

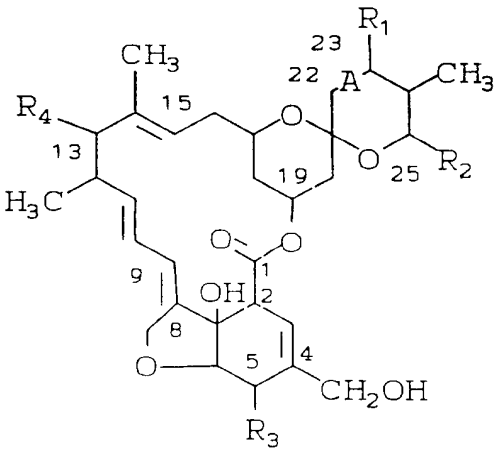
2. A compound of Claim 1 which is 4a-methoxyethoxymethoxy-4"-epi acetyl amino avermectin B1 or 4a-methoxyethoxymethoxy-22,23-dihydro-4"-epiacetylamino avermectin B1 or 4a-methoxyethoxy methoxy-4"-epi-(N-methyl-N-acetylamino) avermectin B1.

3. A compound of Claim 1 which is 4"-epi-N-acetyl-N-methyl amino-4a-hydroxy avermectin B1.

4. A process for the preparation of the compounds of Claim 1 which comprises oxidizing a compound having the formula:

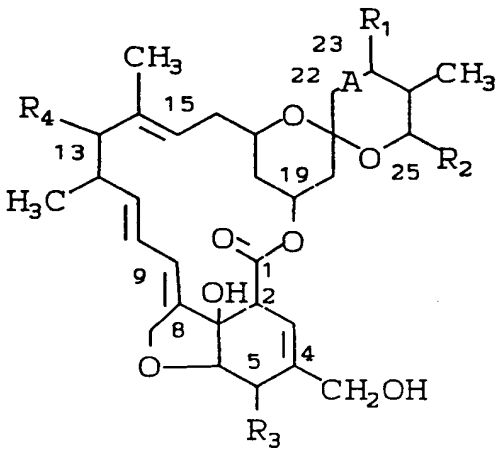


to form a 4a-hydroxy compound having the formula:



which is treated with an acylating reagent or methoxyethoxymethyl halide to form the compound of Claim 1, where R_1, R_2, R_3, R_4 and R_6 are as defined in Claim 1.

5. A process for the preparation of the compounds of Claim 1 where R_6 is other than hydroxy which comprises treating a compound having the formula:



where R_1, R_2, R_3, and R_4 are as defined in Claim 1, with an acylating reagent or methoxyethoxylmethyl.

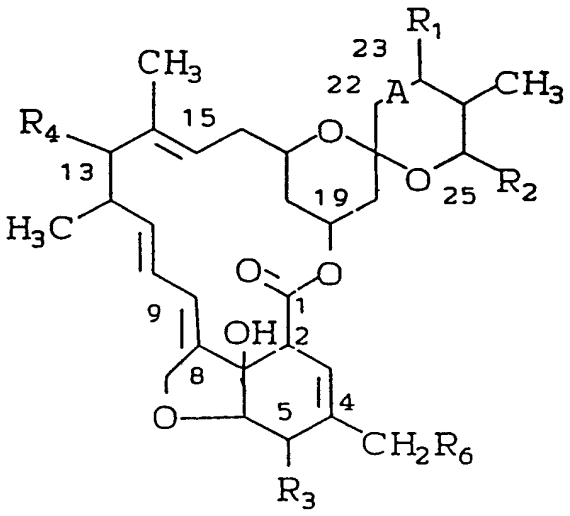
6. A method for the treatment of parasitic infections in plants which comprises treating such plants with an effective amount of a compound of Claim 1.

7. A composition useful for the treatment of parasitic infections in animals and plants which comprises an inert ingredient and a compound of Claim 1.

8. The use of a compound of Claim 1 for the manufacture of a medicament for the treatment of parasitic infections in animals.

Patentansprüche

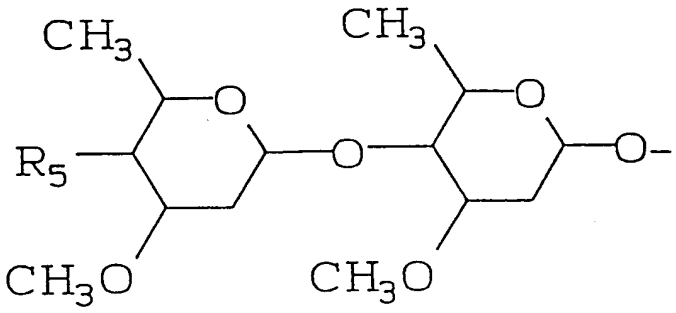
1. Eine Verbindung mit der Formel



worin

A eine 22,23-Einfachbindung oder -Doppelbindung ist, und R_1 Wasserstoff ist,
R_2 Isopropyl oder sek.-Butyl ist,

R_3 Hydroxy ist,
R_4

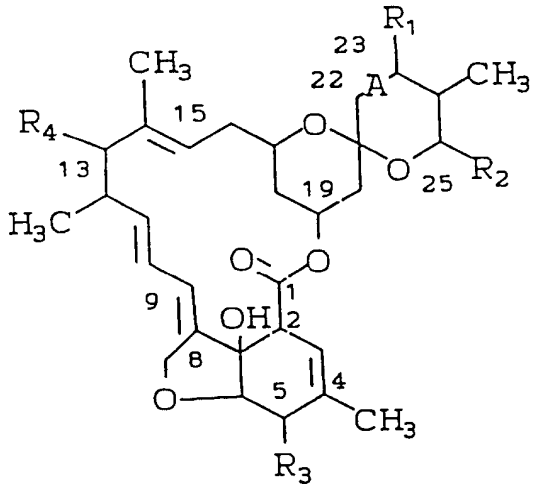


ist, worin
R_5 N-Acetylamino oder N-Methyl-N-acetylamino ist, und
R_6 Hydroxy, Acetoxy, Benzoyloxy, Nicotinoyloxy oder Methoxyethoxymethoxy ist.

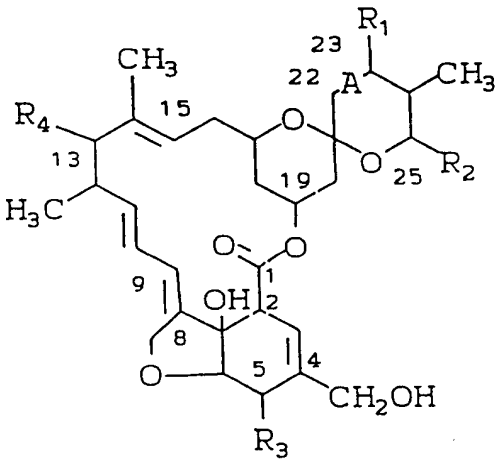
2. Eine Verbindung nach Anspruch 1, die 4a-Methoxyethoxymethoxy-4"-epi-acetylaminoavermectin B1 oder 4a-Methoxyethoxymethoxy-22,23-dihydro-4"-epi-acetylaminoavermectin B1 oder 4a-Methoxyethoxymethoxy-4"-epi-(N-methyl-N-acetylamino)avermectin B1 ist.

3. Eine Verbindung nach Anspruch 1, die 4"-epi-N-acetyl-N-methylamino-4a-hydroxyavermectin B1 ist.

4. Ein Verfahren zur Herstellung der Verbindungen nach Anspruch 1, das Oxidation einer Verbindung mit der Formel:

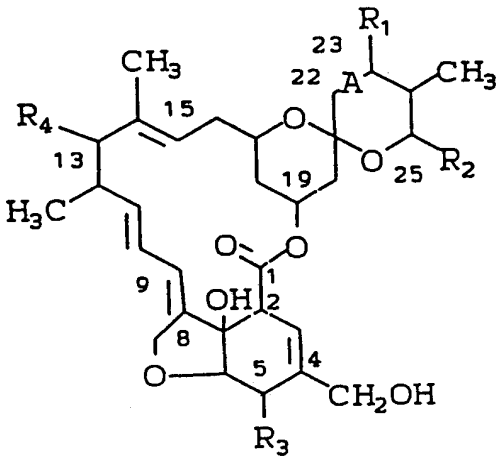


umfaßt, um eine 4a-Hydroxyverbindung mit der Formel:



zu bilden,
die mit einem Acylierungsreagenz oder Methoxyethoxymethylhalogenid behandelt wird, um die Verbindung nach Anspruch 1 zu bilden,, worin R_1, R_2, R_3, R_4 und R_6 wie in Anspruch 1 definiert sind.

5. Ein Verfahren zur Herstellung der Verbindungen nach Anspruch 1, worin R_6 anders als Hydroxy ist, das die Behandlung einer Verbindung mit der Formel:



worin R_1, R_2, R_3 und R_4 wie in Anspruch 1 definiert sind, mit einem Acylierungsreagenz oder Methoxyethoxymethylhalogenid umfaßt.

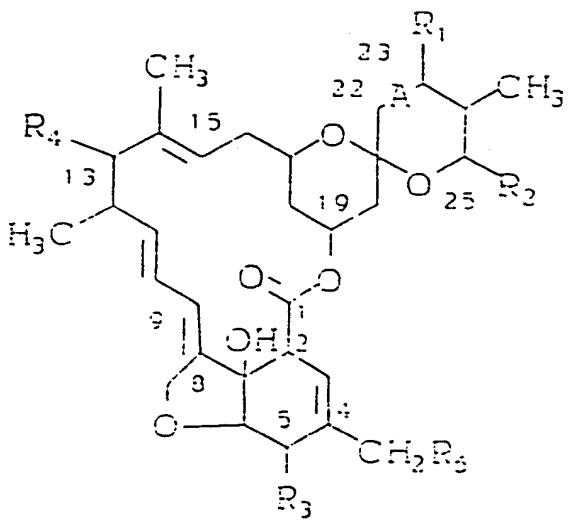
6. Ein Verfahren zur Behandlung parasitärer Infektionen bei Pflanzen, das die Behandlung solcher Pflanzen mit einer wirksamen Menge einer Verbindung nach Anspruch 1 umfaßt.

7. Eine Zusammensetzung, die zur Behandlung parasitärer Infektionen bei Tieren und Pflanzen geeignet ist, die einen inerten Bestandteil und eine Verbindung nach Anspruch 1 enthält.

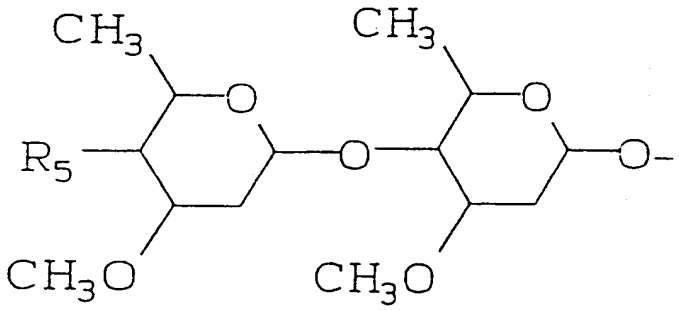
8. Die Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung parasitärer Infektionen bei Tieren.

Revendications

1. Un composé de formule



A représente une liaison 22,23 simple ou double et R_1 représente l'hydrogène ;
R_2 représente un groupe isopropyle ou sec-butyle,
R_3 représente un groupe hydroxy,
R_4 représente le groupe

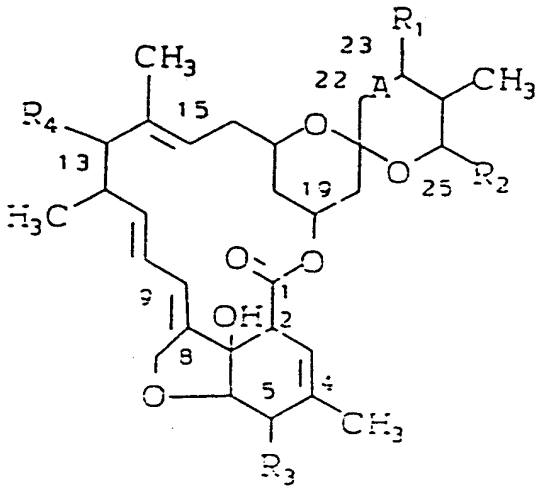


dans lequel
R_5 représente un groupe N-acétylamino ou N-méthyl-N-acétylamino et
R_6 représente un groupe hydroxy, acétoxy, benzoyloxy, nicotinoyloxy ou méthoxyéthoxyméthoxy.

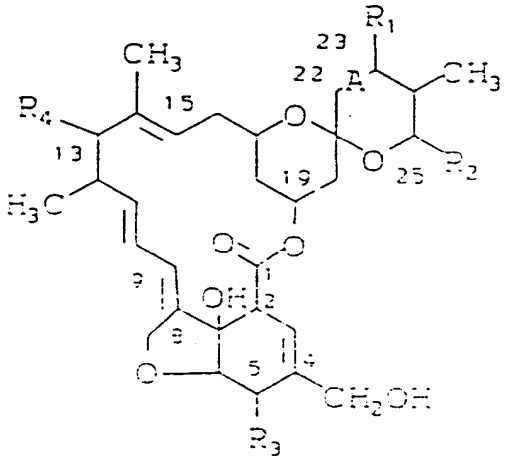
2. Un composé selon revendication 1, qui consiste en la 4a-méthoxyéthoxyméthoxy-4"-épiacétylaminoavermectine B_1 ou la 4a-méthoxyéthoxyméthoxy-22,23-dihydro-4"-épiacétylaminoavermectine B_1 ou la 4a-méthoxyéthoxyméthoxy-4"-épi-(N-méthyl-N-acétylamino)avermectine B_1.

3. Un composé selon revendication 1, qui consiste en la 4"-épi-N-acétyl-N-méthylamino-4a-hydroxyavermectine B_1.

4. Un procédé pour la préparation des composés selon revendication 1 qui consiste à oxyder un composé de formule

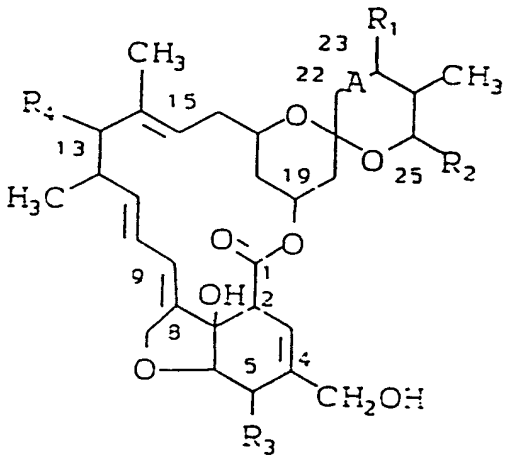


avec formation d'un composé 4a-hydroxylé répondant à la formule



qu'on traite par un réactif acylant ou par un halogénure de méthoxyéthoxyméthyle pour formation d'un composé selon revendication 1 pour lequel R_1, R_2, R_3, R_4 et R_6 ont les significations indiquées dans la revendication 1.

5. Un procédé pour la préparation des composés selon revendication 1 pour lesquels R_6 a une signification autre que le groupe hydroxy, qui consiste à traiter un composé répondant à la formule



dans laquelle R_1, R_2, R_3 et R_4 ont les significations indiquées dans la revendication 1, par un réactif acylant ou un halogénure de méthoxyéthoxyméthyle.

6. Un procédé pour le traitement des infections parasitaires des végétaux, qui consiste à traiter les végétaux par une quantité efficace d'un composé selon revendication 1.

7. Une composition utile pour le traitement des infections parasitaires des animaux et des végétaux, qui consiste en un composant inerte et un composé selon revendication 1.

8. L'utilisation d'un composé selon revendication 1 pour la préparation d'un médicament prévu pour le traitement des maladies parasitaires des animaux.